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SYNTHESIS OF HIGH PURE TICAGRELOR, AN ANTI-PLATELET DRUG SUBSTANCE AND ITS POSSIBLE PROCESS RELATED IMPURITIES

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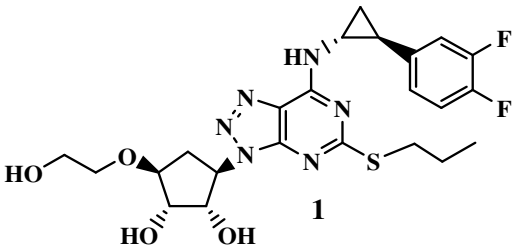
ABSTRACT

Cost effective, robust manufacturing process is developed for N-alkylation of compound **6** and **7** with commercially available reagent/base like DBU, TEA and ethanol used as a solvent. The most important development is high pure pharma product Ticagrelor was achieved by purifying in mixture of Methanol and Water. As per ICH guidelines all known and unknown impurities limits below NMT 0.10% achieved with excellent yield (75%) and Quality 99.9%.

Keywords: synthesis, high pure, cost effective, N-alkylation, DBU, Ticagrelor

INTRODUCTION

Ticagrelor is a platelet inhibitor[1-3] with chemical name (1S,2S,3R,5S)-3-[7-{[(1R,2S)-2-(3,4-difluorophenyl)cyclopropyl]amino}-5 (propylthio)-3H-[1,2,3]-triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol, Molecular formula, Molecular weight $C_{23}H_{28}F_2N_6O_4S$ and 522.57 respectively.



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Chemical Structure: Ticagrelor

Ticagrelor (TGL) was developed by AstraZeneca Company in 1999, since from discovery several kinds of literature were published among those few of are having very important in the development of TGL. David hardem et al[4] reported the synthesis of Ticagrelor which is comprises the steps of reacting 4, 6-dichloro-5-nitro-2-(propylthio) pyrimidine with cyclopentyl intermediate followed by reducing the obtained intermediate in an iron powder/acetic acid system; ring closing of the resulting product in the presence of a nitrite; and finally carrying out a series of reactions, including ammonization, bromination and substitution reaction (Scheme-1).

The method has a prolonged route, wherein due to the strong electron-withdrawing effect of the nitro group, the chlorines on positions 4, 6 of 4,6-dichloro-5-nitro-2-(propylthio)pyrimidine are of high activity, and are readily reacted with the amino group and the hydroxyl group of the cyclopropyl

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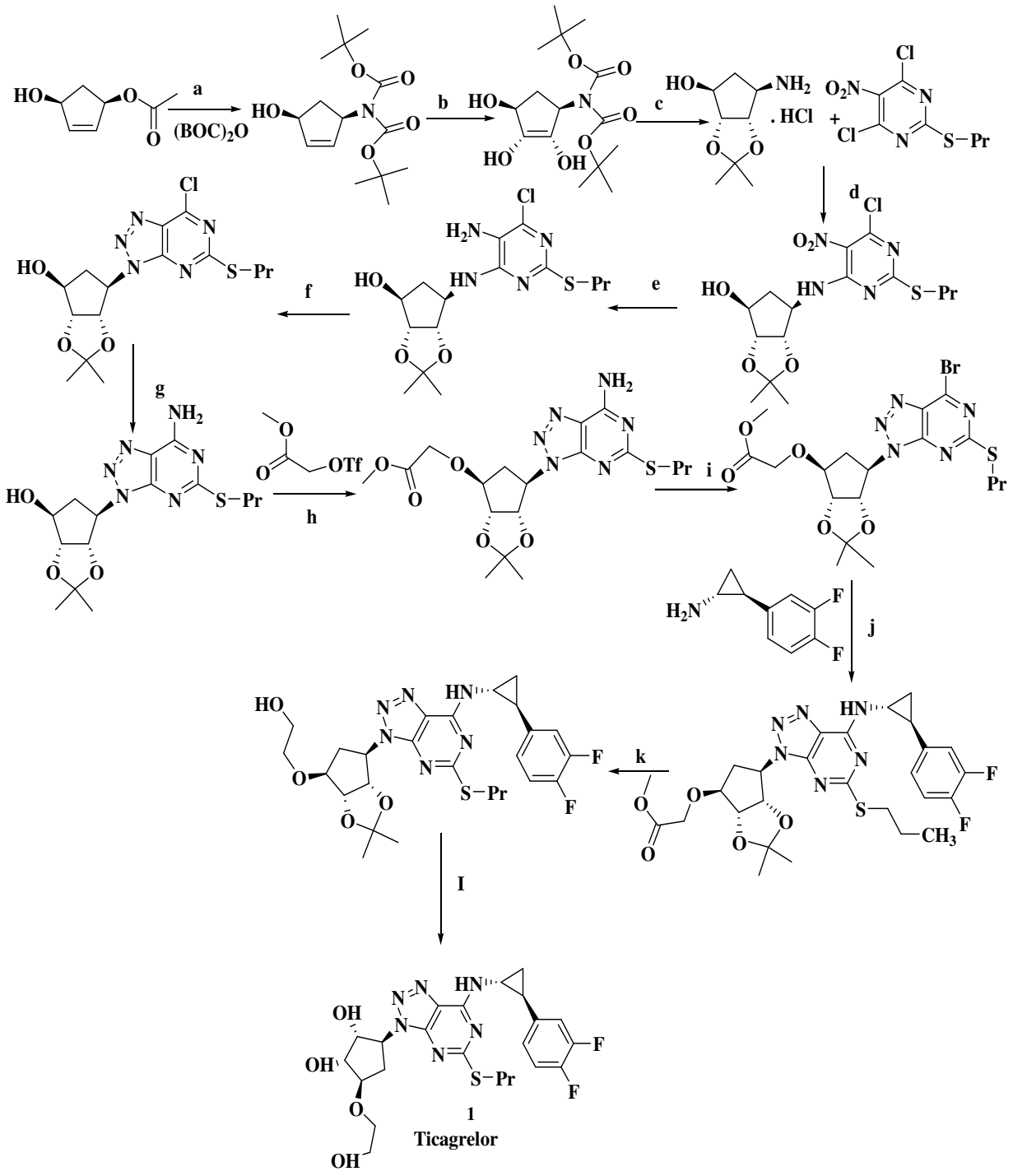
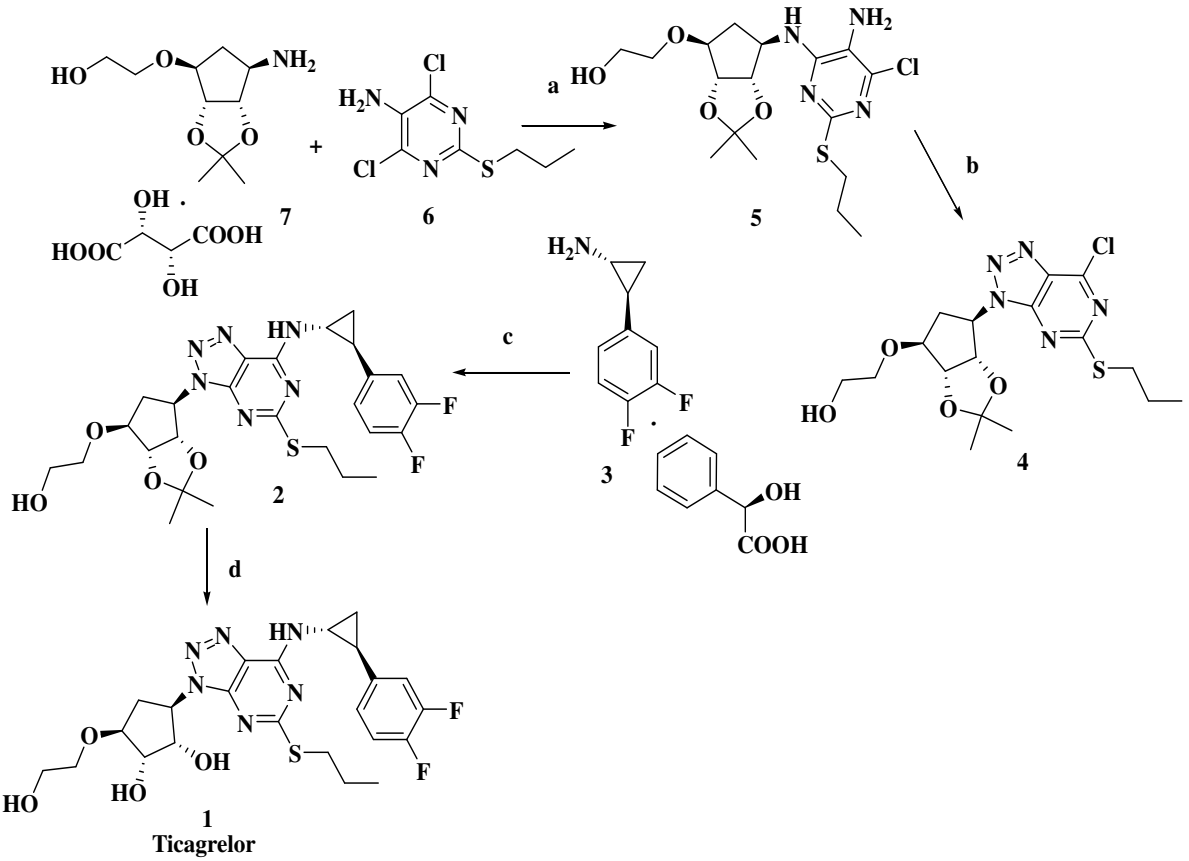
intermediate. The reaction system is typically complicated, and the resulting intermediate is difficult to purify. The entire route involves many reactions under harsh conditions, such as bromination, amination and the application of butyl lithium reagent is not suitable for industrial scale up. In view of all of these, together with other disadvantages, it is clear that the route is not suitable for production.



Scheme-1: Reagents and solvents; (a) NaH/THF; Pd $(PPh_3)_4$; (b) THF/NMP/OSO_4/$Na_2S_2O_2$; (c) Dimethoxypropane/8M HCl/MeOH; (d) iPr_2NEt/THF; (e) Fe/AcOH; (f) Isoamyl Nitrile/ACN, 70°C ; (g) THF/NH_3; (h) n-BuLi/THF; (i) Isoamylnitrile /$CHBr_3$; (j) iPr_2NEt/MDC, 16 hour; (k) DIBAL-H/THF; (l) TFA/H_2O.



Scheme-2: Reagents and solvents: (a) Ethanol, TEA and DBU (b) ethyl acetate $NaNO_2$/Acetic acid (c) Sodium Carbonate (d) Methanol and dil. HCl

Synthesis of Compound -7 of Scheme-2 was reported with the justified route of synthesis[2, 5, 6], The N-alkylation reaction was reported [7, 8] in various organic bases like DIPEA, TEA, and inorganic bases like Potassium carbonate in solvents media like Tetrahydrofuran, Ethyl acetate etc.,. But none of the methods was explored with DBU and Triethylamine in Ethanol combination for conversation of compound 7 and 6 to compound 5.

In the final step as per current regulatory guidelines, any other individual and known or unknown process-related impurities should be less than 0.10%. Therefore we tried different purification methods to remove known TGL hydroxyl impurity (**10**) and TGL diastereoisomers impurity (**11**) TGL Acetyl impurity (**12**), TGL-Amine impurity (**13**), TGL Sulfoxide impurity (**14**) with available literature procedures[9-12], but always optioned border case results. Then we identified a new solvent combination of Methanol and Water (1:2) to purify the crude Ticagrelor (TGL) drug substance and achieved consistent results with respect to the yield & quality. The all impurities what we are facing earlier were not a concern now with new pure purification method and is nowhere reported and hence it is novel. Final crystallization is doing in Acetonitrile to attain desired prior art Form-III of Ticagrelor.

As discussed above all possible impurities were synthesized, characterized and spiked in the respective HPLC methods to confirm the retention times of each individual impurity. The route of synthesis of explored impurities and their procedures were incorporated in the following sections.

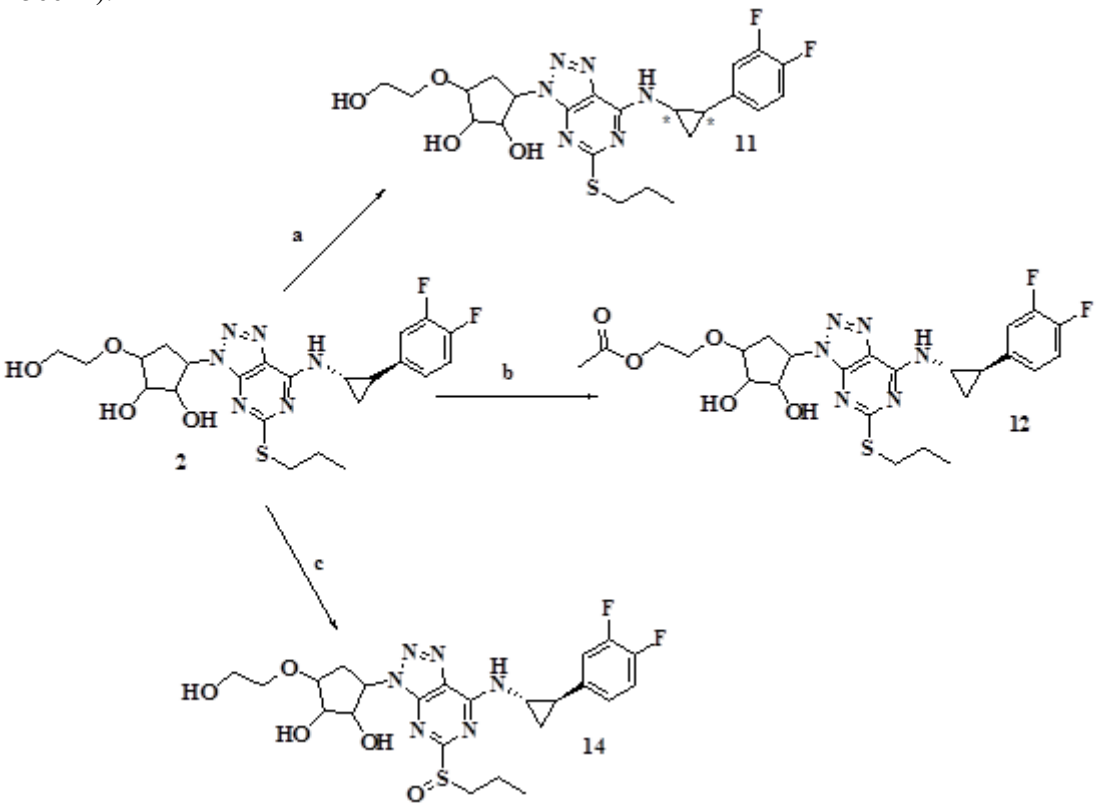
EXPERIMENTAL

Materials and Methods

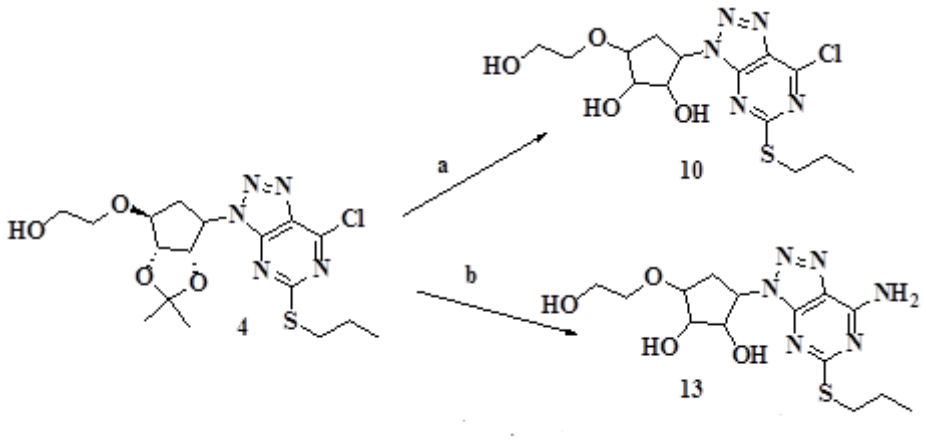
The raw materials used for its selected route of synthesis (Scheme II) is procured from commercial good manufacturing sources, and the reagent grade materials were purchased from commercially available and from approved manufacturing sources. All the solvents used for its entire Ticagrelor process development were procured from commercial solvent suppliers.

Synthesis Of 2-((3aS, 4R, 6S, 6aR)-4-(5-amino-6-chloro-2-(propylthio) pyrimidin-4-ylamino)-tetrahydro-2, 2-dimethyl-3aH-cyclopenta[d][1,3]dioxol-6-yloxy)ethanol (5)

In a 500 mL dry round bottom flask, To stirred solution of (100 ml) ethanol, added 100gm of compound 7 at room temperature, followed by the addition of 60gm of the compound- 6, 105gms of Triethylamine and 110gms of DBU. The temperature of the reaction mass was raised to reflux, and maintained for 2-3 hours. After completion of the reaction in the TLC method, the reaction mass was cooled to room temperature and then 300ml of HCl was added, the whole reaction mass was extracted with ethyl acetate (3 x 300ml).



Scheme-3: (a) Conc. HCl, Methanol, (b) Acetic Acid, Acetic Anhydride, (c) Acetic Acid, 30% H_2O_2



Scheme-4: (a) 15% Metanolic / HCl, (b) NH_4OH/ Methanol/ HCl

The combined organic layers were washed with saturated brine solution, and finally dried over anhydrous sodium sulphate; the crude obtained was crystallized in n-hexane to obtain pure compound -5, Yield 80-

85%, purity 98.8%. Spectral characterization data: 1H NMR: δ 6.57 (d, 1H), δ 5.01(s, 1H), δ 4.74 (s, 2H), δ 4.52 (d, 1H), δ4.47 (d, 1H), δ 4.30 (d, 1H), δ 3.86 (d, 1H), δ 3.50 (m, 4H), δ 2.97 (d, 2H), δ 2.22 (m, 1H), δ 1.88 (d, 1H), δ 1.63 (m, 1H), δ 1.36 (s, 3H), δ 1.20 (s, 3H), δ 0.94 (t, 3H); ^{13}C NMR:155.76, 151.91, 138.48, 119.76, 109.96, 84.16, 83.75, 83.20, 70.35, 60.38, 56.64, 32.76, 32.14, 26.32, 23.97, 22.94, 13.28; FT-IR(Cm^{-1}): 3436, 3246, 3384, 3352, 2955, 2869, 1643, 1567, 1480, 1460, 1265, 1207, 1375, 1309, 1189, 1162, 1122, 854, 819; Mass (m/z): 419.28

Synthesis of 2-((3aS, 4R, 6S, 6aR)-4-(7-chloro-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-tetrahydro-2,2-dimethyl-3aH-cyclopenta[d][1,3]dioxol-6-yloxy)ethanol(4)

In a 1000mL dry round bottom flask, added 100gms of compound-5 to a solution of 500ml of ethyl acetate, 90gms of Acetic acid and 20% aqueous Sodium nitrite solution at room temperature. Then cooled the reaction mass temperature and was maintained for 5hrs at 10-15ºC. After TLC is complies the reaction mass was adjusted with pH~5 with NaOH solution. The layers were separated; organic layer was dried with sodium sulphate and removed the solvent to attained desired compound-4. Yield: 90-95%. Spectral characterization data: 1H NMR: δ 9.39 (d, 1H), δ 7.26-7.35(m, 2H), δ 4.99 (m, 1H), δ 4.62-4.67 (m, 1H), δ 4.54 (bs,1H), δ 3.98 (bs, 1H), δ 3.38-3.48 (m, 5H), δ 3.13 (m, 1H), δ 2.87 (q, 2H), δ 2.63 (m, 1H), δ 2.11 (bm,1H), δ 1.48-1.55 (m, 2H), δ 1.46 (s, 6H), δ 1.33-1.42 (m, 1H), δ 1.24 (m, 1H), δ 0.81 (t, 3H); ^{13}C NMR:169.48, 153.91, 150.52, 149.03, 148.21, 139.18, 123.13, 122.13, 117.04, 114.96, 112.41, 83.72, 82.02, 70.68, 61.38, 60.04, 35.44, 33.98, 32.36, 26.83, 24.69, 23.94, 14.90, 13.02; FT-IR(Cm^{-1}): 3294, 3119, 3050, 2934, 2873, 1616, 1590, 1520, 1430, 1455, 1327, 1275, 1211, 1058, 863, 771; Mass (m/z): 563.33.

Synthesis of 2-((3aS,4R,6S,6aR)-4-(7-((1R, 2S)-2-(3,4-difluorophenyl)cyclopropyl amino)-5-(propylthio)-3H- [1, 2, 3] Triazolo [4, 5-d]pyrimidin-3-yl)-tetrahydro-2, 2-dimethyl-3aH-cyclopenta [d] [1, 3] dioxol-6-yloxy)ethanol (2)

In a 100mL dry round bottom flask, 90gms of compound-4 was added to a mixture solution of 500ml of ethyl acetate, 80gms of compound-3 and followed by 80gms of sodium carbonate was added. The reaction mass was stirred at room temperature for 3-4 hours and check the TLC, once TLC complies, the reaction mass was quenched with 700ml of Water. The layers were separated. The obtained Organic layer was dried over sodium sulphate. Remove the organic solvent under reduced pressure to obtain the desired compound -2.Yield: 90%.

Synthesis of (1S,2S,3R,5S)-3-(7-((1R,2S)-2-(3,4-difluorophenyl)cyclopropylamino)-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-5-(2-hydroxyethoxy)cyclopentane-1,2-diol (1), TGL

To a dry & clean 5000mL round bottom flask, added 1000mL of Conc. Hydrochloric acid and 200 gm of compound 2 at room temperature. Slowly raised the reaction mass temperature to 60-65 ^{0}C with vigorous stirring, the entire reaction mass was maintained for 3 hours at the same temperature. Once TLC complies cooled the reaction mass temperature to room temperature and then slowly adjusted the pH to 7.0-8.0 by with 40% Sodium Hydroxide solution (600mL). The basic reaction mass was precipitated with slow addition of Methanol (400 mL) as anti-solvent and the precipitated reaction mass was maintained for 60 minutes. The obtained filtered cake was washed with Water (150 mL) and dried for 40-45^{0}C for 2-3 hours and afforded solid compound 1 crude weight was 100gm.

Purification with Mixture of Water in Methanol

To a solution of 500ml of Methanol in the 80gms of compound-2, was added 6N of dilute HCl which was stirred for 7hours at room temperature, pH was adjusted with NaOH solution, Ticagrelor was isolated from the reaction mass. Yield: 85-90%.

Purification with Pure Acetonitrile

In a clean and dry 1000 mL round bottom flask, 60grms of crude Ticagrelor and 500ml of Acetonitrile was taken, then this solution was heated to reflux for 1-2 hours, then cooled to the room temperature, and filtered the material to obtain high pure Ticagrelor. Yield: 85-90%. Purity: 99.85% by HPLC with single maximum impurity less than 0.1%. Spectral characterization data: 1H NMR: δ 9.35 (d, 1H), δ 7.30 (m,

2H), δ 7.05 (d, 1H), δ 5.10 (d, 1H), δ 5.05 (d, 1H), δ 4.98 (m, 1H), δ 4.57 (m, 1H), δ 3.93(d, 1H), δ 3.46 (m, 4H), δ 3.12 (m, 1H), δ 2.91 (m, 2H), δ 2.63 (m, 1H), δ 2.12 (t,1H), δ 2.05 (m,1H), δ 1.51(m, 2H), δ 1.36 (q, 1H), δ 0.78-0.81 (t, 3H); ^{13}C NMR:169.28, 154.00, 150.52, 149.48, 139.26, 123.24, 122.75, 117.08, 114.97, 81.88, 74.44, 73.82, 70.92, 60.63, 60.40, 34.09, 33.28, 32.42, 24.07, 22.34, 15.01; FT-IR(Cm^{-1}): 3294, 3119, 3050, 2934, 2873, 1616, 1590, 1520, 1430, 1455, 1327, 1275, 1211, 1058, 863, 771; Mass (m/z): 523.34

Synthesis of (1S,2S,3S,5R)-3-(2-hydroxyethoxy)-5-(7-hydroxy-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)cyclopentane-1,2-diol (10)

In a dry and clean round bottom flask added 27 gm of crude compound 4 and 88 mL of 6N hydrochloric acid solution under gentle stirring. Maintain the reaction mass at room temperature for 11-12 hours. Reaction mass pH was adjusted to 8-9 with 20% Sodium hydroxide solution (125 mL). Again maintain the reaction for 2-3 hours with gentle stirring, Once TLC completed. The Reaction mass was distilled under reduced pressure to remove Water. The obtained crude mass pH was further adjusted to 2-3 with Conc. Hydrochloric acid (60 mL), cool the reaction mass 10-15 ^{0}C and maintain for 20 minutes. Filter the reaction mass, the filtered cake was washed with 10 mL of water and dried over vacuum oven for 2 hours to afford the desired TGL hydroxyl impurity (10). Spectral characterization data: 1H NMR: δ 5.14(bs, 1H), δ 5.00 (bs, 1H), ,δ 4.80 (bq, 1H), δ 4.62 (s, 1H), δ4.50 (s, 1H), δ 3.92 (s, 1H), δ 3.73 (s,1H), δ3.37-3.48 (m, 6H), δ 2.96 (bq, 2H), δ 1.99 (bt, 1H), δ 1.62 (m, 2H), δ 0.94 (t, 3H); ^{13}C NMR: 168.10, 164.61, 150.60, 128.81, 81.96, 73.96, 70.72, 60.26, 32.97, 31.99, 22.79, 13.32; FT-IR(Cm^{-1}): 3415, 2916, 1322, 1224; Mass (m/z): 370.0

Synthesis of (1S,2S,3R,5S)-3-(7-(2-(3,4-difluorophenyl)cyclopropylamino)-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-5-(2-hydroxyethoxy)cyclopentane-1,2-diol (11)

To a dry & clean 500mL round bottom flask, added 100mL of Conc. Hydrochloric acid and 20gm of compound 2 at room temperature. Slowly raised the reaction mass temperature to 60-65 ^{0}C with vigorous stirring, the entire reaction mass was maintained for 5 hours at the same temperature. Once TLC complies cooled the reaction mass temperature to room temperature and then slowly adjusted the pH to 7.0-8.0 by with 40% Sodium Hydroxide solution (60mL). The basic reaction mass was precipitated with slow addition of Methanol (40 mL) as anti-solvent and the precipitated reaction mass was maintained for 60 minutes. The obtained filtered cake was washed with Water (15 mL) and dried for 40-45^{0}C for 2-3 hours and afforded solid weight was 10gm. Spectral characterization data: : 1H NMR: δ 8.11 (s, 1H), δ 8.02 (s, 1H), δ 7.40 (q, 2H), δ 7.21 (t, 3H), δ 4.47 (s, 2H), δ 4.45 (s, 1H), δ 4.43 (s, 1H), δ 4.10 (s, 1H), δ 4.05 (q, 1H), δ 3.95 (s, 1H), δ 3.79 (s, 1H), δ 3.38-3.47 (t, 6H), δ 3.06 (q, 1H), δ 2.82 (q, 2H), δ 2.79 (m, 1H), δ 2.05 (t,2H), δ 2.04 (m,1H), δ 1.64 (q, 2H), δ 0.91 (t, 3H); ^{13}C NMR: 169.50, 168.82, 154.38, 150.64, 148.21, 123.49, 122.77, 117.17, 115.38, 82.36, 73.94, 70.57, 60.28, 56.74, 34.62, 32.35, 32.00, 23.05, 22.57; FT-IR (Cm^{-1}): 3438, 3303, 2935, 1327, 1219; Mass (m/z): 523.00.

Synthesis of 2-((1S,2S,3S,4R)-4-(7-((1R,2S)-2-(3,4-difluorophenyl)cyclopropylamino)-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-2,3-dihydroxycyclopentyloxy)ethyl acetate (12)

In a 500mL round bottom flask**,** To a cooled solution of 10mg of compound 2 in 70mL of chloroform, added Anhydrous Aluminium chloride (7.65gm) and Acetic acid (10mL) at 10-15^{0}C . After maintained 10 minutes, acetic anhydride was added slowly over a period of 10-15 minutes. The reaction mass was maintained for 3-4 hours at room temperature, TLC monitored to see the progress of the reaction. Once reaction complies, removed the solvent under reduced pressure and the obtained crude mass was quenched in water (30 mL) and extracted with Methylene dichloride (3 x 50mL), The combined organic layers were washed with brine and then dried over an hydrous sodium sulphate (2gm). The obtained crude material after distillation was subjected for column purification Methanol / chloroform used as a mobile phase to yielded 5gm.

Spectral characterization data: 1H NMR: δ 7.33 (s, 2H), δ 7.28 (s, 1H), δ 5.11 (s, 1H), δ 4.94 (q, 1H), δ 4.54 (s, 1H), δ 4.11(s, 1H), δ 3.92 (s, 1H), δ 3.76 (s, 1H), δ 3.12-3.30 (t, 6H), δ 3.06 (q, 1H), δ 2.91 (q, 2H), δ 2.85 (t, 1H), δ 2.11 (t, 1H), δ 2.01 (t, 2H), δ 1.50 (q, 2H), δ 0.97 (t, 3H), δ 0.80 (s, 3H);; ^{13}C NMR:

170.26, 169.11, 150.60, 153.89, 148.17, 123.11, 122.75, 117.04, 114.72, 81.74, 74.17, 73.72, 66.75, 63.21, 60.52, 33.96, 32.95, 26.76, 22.22, 13.13, 12.88; FT-IR (Cm^{-1}): 3267, 2964, 1741, 1321, 1196; Mass (m/z): 565.00.

Synthesis of (1S,2S,3S,5R)-3-(2-hydroxyethoxy)-5-(7-amino-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)cyclopentane-1,2-diol (13)

5 gm of Compound 4 was taken in a 500mL round bottom flask, added 20mL of 15% aq. Ammonia solution, stirred for 15 hours at room temperature. After completion of the TLC, the reaction mass was diluted with Water 20mL and Extracted with Ethyl acetate (3 X 20mL). The combined organic layers were washed with brine solution (20mL), dried over anhydrous sodium sulphate and removed the solvent under reduced pressure. The obtained crude Amine was purified in MTBE solvent to afford 2 gm of pure compound 13. Spectral characterization data: 1H NMR: δ 5.09 (s, 1H), δ 5.02 (s, 1H), ,δ 4.98 (q, 1H), δ 4.58 (s, 1H), δ4.56 (s, 1H), δ 3.93 (s, 1H), δ 3.74 (s,1H), δ3.30-3.50 (m, 6H), δ 3.06 (q, 2H), δ 2.05 (t, 1H), δ 1.66 (q, 2H), δ 0.97 (t, 3H); ^{13}C NMR: 169.03, 155.06,149.60, 122.78, 81.75, 74.02, 70.74, 60.24, 32.99, 32.07, 22.33, 13.17; FT-IR(Cm^{-1}): 3412, 3178, 2931, 1321, 1220, ; Mass (m/z): 371.0

Synthesis of (1S,2S,3R,5S)-3-(7-((1R,2S)-2-(3,4-difluorophenyl)cyclopropylamino)-5-(propylsulfinyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-5-(2-hydroxyethoxy)cyclopentane-1,2-diol (14)

10mL glacial Acetic acid was taken in a 500mL clean and dry round bottom flask, added 5 gm of compound 2 and this reaction mass was stirred for 20 minutes at room temperature. Then the Cooled to 10-15^{0}C, slowly added 100 mL of 30% Aq. Hydrogen peroxide solution drop wise(it took 10 minutes) with gentle stirring and slowly raised the temperature to 60-65^{0}C. After 2 hours maintenance reaction mass was cooled to room temperature, further diluted with Water 100mL, Filtered the precipitated solid, washed with another 25mL Water and The obtained solid was dried for 2-3 hours under vacuum. The crude material was re-crystalized in Methanol and dried to yielded 2gm. Spectral characterization data: 1H NMR: δ 9.84 (d, 1H), δ 7.23-7.36 (m, 2H), δ 7.04 (s, 1H), δ 5.03-5.18 (m, 2H), δ 4.59-4.62 (m, 1H), δ4..49-4.58 (m, 1H), δ 3.96 (bm, 2H), δ 3.75-3.78 (bm,2H), δ3.45-3.51 (m, 1H), δ3.16-3.20 (m, 1H), δ3.02-3.09 (m, 1H), δ 2.90-2.99 (m, 2H), δ 2.84 (t, 1H), δ 2.63-2.73 (m, 1H), δ 1.97-2.09 (m, 1H), δ 1.54-1.76 (m, 2H), δ 0.87 (t, 2H), δ 0.81 (t, 3H); ^{13}C NMR: 170.76, 154.96, 149.28, 139.13, 124.45, 122.82, 117.14, 115.05, 81.71, 75.05, 73.61, 70.87, 60.46, 54.76, 35.81, 33.83, 33.54, 24.02, 14.55, 12.96; FT-IR(Cm^{-1}): 3477, 3281, 2935, 2963, 2877, 3011, 3047, 1428, 1389, 1277, 1214, 1115, 1065, 773, 890; Mass (m/z): 539.1.

RESULTS AND DISCUSSION

After revealing all the literature methods for N-alkylation of compound 7, it is understood that all the reported conditions are taking more time for its conversion and we observed few workup issues. Then we taught that that kind of procedure may not suitable for commercial level execution, in-plant we may face some unforeseen workup issues. After exploring several bases with various solvents and at different conditions (as shown in the Table-1), we developed a new N-Alkylation process to overcome all these issues. The N-alkylation process which involves the preparation of Ticagrelor intermediate (compound-5) by reacting compound-7 with compound-6 in Ethanol and in the presence of TEA and DBU mixture which yield the highly pure intermediate of compound-5. The rate of impurity formation is very low in the said process and with good quality.

The feasibility studies of N-Alkylation to get optimal conditions as shown as in the below table, the only one condition is good with respect to yield & quality such as DBU & TEA in Ethanol.

The above-said process-related impurities were identified, synthesized and characterized with the help of 1H, 13C NMR, Mass and FT-IR. The methods used for their syntheses, which were newly developed, these impurities were demonstrated in TGL HPLC validated method and their detailed experimental procedures were given in the above experimental section.

CONCLUSION

A Cost-effective N-Alkylation process, a novel purification method was developed, optimized and controlled all the process related impurities with in their specified Limit as per ICH guidelines. As per as

all the literature is a concern, This process is unique and commercially feasible to get high pure Ticagrelor drug substance with over all yield 75%, HPLC Purity NLT 99% and Single Maximum impurity limit NMT 0.1%.

Table-1: N-Alkylation Feasibility Reactions Results

S. No.	Solvent	Base	Yield (%)	Purity (Area %)
1.	1,4-dioxane	TEA	70.0	99.04
2.	Dichloromethane	K_2CO_3	--	No reaction
3.	DMF	DIPEA	26.43	90.88
4.	Ethanol	TEA+DBU	80.7	99.6
5.	THF	DIPEA	--	No reaction
6.	Water	Na_2CO_3	78.9	98.36
7.	Water and EtOH	Na_2CO_3	48.2	98.47
8.	Water and IPA	Na_2CO_3	48.2	90.16
9.	Water and Toluene	Na_2CO_3	70.2	94.48
10.	Neat	TEA +DBU	61.4	98.29

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